INTERNATIONAL JOURNAL OF PHARMACEUTICAL, CHEMICAL AND BIOLOGICAL SCIENCES

Available online at www.ijpcbs.com

Research Article

SYNTHESIS OF 1, 2 DI-SUBSTITUTED QUINAZOLINONE DERIVATIVES AND THEIR ANTI-MICROBIAL SCREENING

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ABSTRACT

Quinazolinone is a compound made up of two fused six member simple aromatic benzene ring and a number of substituted quinazolinone are known for their biological importance like anti-cancer, anti-biotic, anti-microbial, anti-HIV, anti-oxidant, anti-tubercular, anti-malarial, anti-viral, anti-psychotics and anti-inflammatory activity. In the present investigation an attempt has been made for the 1,2 di-substituted quinazolinone, using N-substituted derivative of aniline & derivative of aldehyde. Further these 1,2 di-substituted quinazolinone has condensed with various primary amine containing drug like acetamide, sulfanilamide, thiourea and with aromatic amine like o-chloro benzoic acid, derivative of aniline and derivative of aldehyde. The synthesized compound have been established on the basis of Infra-Red, Nuclear Magnetic Resonance spectral data, Thin Layer Chromatography and Melting Point or Boiling Point .These compound are also screened for biological activity like anti-microbial activity using standard disk method by measuring inhibition of zone. Ceftriaxone was used as standard drug. The synthesized compound was shown to good anti-microbial activity as compared with standard.

Keywords: Ulman condensation reaction, 1,2 di-substituted quinazolinone.

1. INTRODUCTION

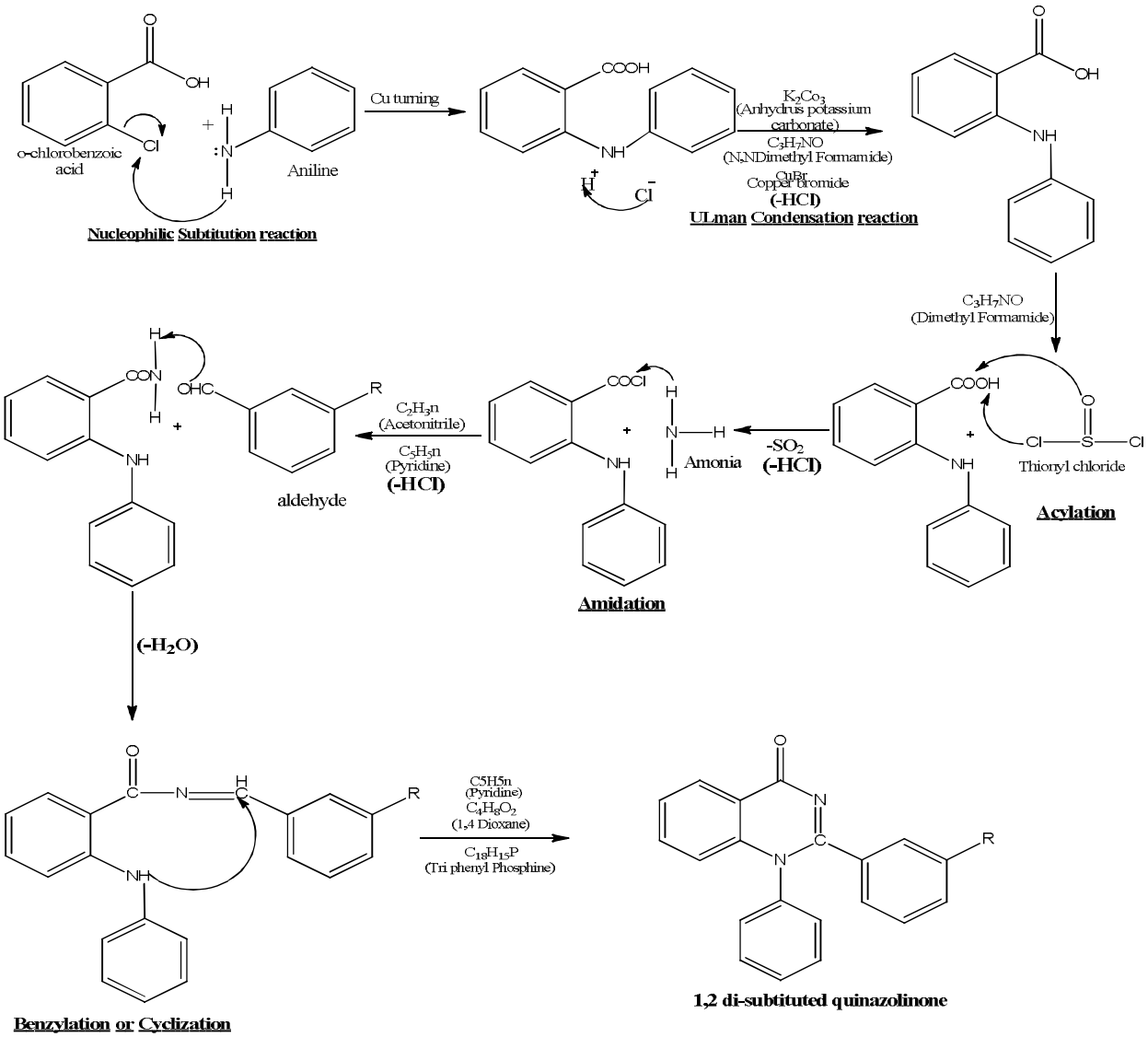
Quinazolinone is one of the most important and prosperous structures in medicinal chemistry. Quinazolinone derivatives have been used in medicine as antibacterial, antifungal, anti-tuberculosis, anticancer and anti-inflammatory agents. The increased rate of resistance to ongoing antimicrobial agents and advent of durable tumor cell to a wide range of cytotoxic drugs inspired us to search for more effective agents. Quinazolinones have emerged as antimicrobial agents because of their broad spectrum of in vitro and in vivo chemotherapeutic activities. Quinazolinone and their derivatives are naturally occurring plant nearly 150 families from a number of different microorganisms and animals are the building blocks for alkaloids. In light of the growing number of applications in recent years, and their bioactivity Quinazolinone derivatives synthesis chemists and biologists in the middle of huge increase in interest. 4 (3H)-containing compounds (Giri RS et al 2009; Jessy EM et al 2007; Chen K.et al 2006; B.S.Furniss et al 2000; Hosakere et al 2010; tiwari AK et al 2007; Grover G et al 2006; Mhaske SB et al 2006; Mahato SB et al 2011), quinazolinone derivatives, including their therapeutic importance (Armarego et al 1967), Anti-cancer activity(Nagwa MAG et al 2010), Anti-HIV activity (Pandey SN et al 1999), Anti-malarial activity (Werbel LM et al 1987), Anti-fungal activity (Ghorab MM et al 2000), Anti-inflammatory activity (Kumar.B et al 2003; Balakumar C et al 2010), Anti-convulsant activity (Aly MM et al 2010), Anti-bacterial activity (Cakici et al 2010), Analgesic activity (Hemalatha et al 2010), Anti-oxidant activity (Selvam TP et al 2010), Anti-mutagenic activity (Kohil D et al 2009), Cns depressant activity (Jatav V et al 2008; Kashawa et al 2009), Anti-leishmanial activity (Aggarwal KC et al 2003), Anti-leukemic activity (Raffa D. et al 2004), Anti-coccidial activity (Ye C et al 2010), Anti-tubercular activity (Wasiser K et al 2007), Anti-hypertensive activity & Anti-hyperlipidemic

activity (Kurogi Y et al 1996), clinical treatments (El-Helby AA et al 1995). Quinazolinone drug discovery and drug development is considered as a privileged scaffold. (3H) Quinazolinone being more common, show different biological activities and its major application in the medical field proven - quinazolinone, 4 In addition to the two Isomers. Quinazolinone anti-derivatives, antihypertensive, NSAID, heart, compelling and were proven to be useful in anti-foliate drug discovery (Aroro et al 2010). The structures of the compounds synthesized were assigned on the basis of elemental analysis, IR, 1H NMR, and anti-microbial activity.

2. MATERIALS AND METHODS

The entire chemicals used were procured from CENTRAL DRUG HOUSE (P) LIMITETED New Delhi. Purity of starting materials used for reaction was confirmed by checking their melting point or boiling point and Thin Layer Chromatography.IR Spectras were recorded in KBr on shimatzu IR 8400 spectrophotometer. ^1H NMR spectra of synthesized compound were recorded on "^1H NMR BRUCKER" spectrometer at 400 MHz frequency in (DMSO). The starting compound o-chloro benzoic acid and aniline has been prepared according to known method.

2.1 Mechanism of reaction scheme



2.2 Procedure

Step I

A mixture o-chloro benzoic acid (0.10 Mole), diffrent aniline (0.17 Mole), anhydrous potassium carbonate (0.17 Mole), copper Powder (Dust) (50 mg) & N,N-dimethyl formamide (40 ml) was refluxed for 3.5 to 6 hrs. During reflux add 50 mg of copper bromide (in 3 times interval).

Cool → Pour in 1N HCl → Stir → Filter → Wash with water
Grey Solid ← Dry ← Recrystallise

Step II

A mixture of (I) (0.1 Mole), thionyl Chloride (0.2 Mole) and Ammonia (0.2 Mole) in 10 ml of Dimethyl Formamide was reflux for 1-2 hrs to obtained Amide.

Residue → Cool → Filter & Dry → Recrystallise

Step III

A mixture of (II) (20 Mili Mole) are added with m-chloro benzaldehyde (20 Mili Mole) & Glacial acetic acid (15-20 ml) are reflux with water bath for 3-5 hrs.

Cool → Filter & Dry → Recrystallise

2.3 Synthesis of KFa

IR (KBr, cm^{-1}): 3047.5 (aromatic CH str.), 1691.6 (C=O), 692.23 (C-Cl), 600 (Br); **^{1}H NMR (DMSO, δ (ppm)):** 6.79-8.89 (6H, aromatic ring); **R_f value:** 0.28; **Boiling point:** 195^{o}C; **Percentage yield:** 82%.

2.4 Synthesis of KFb

IR (KBr, cm^{-1}): 3047.5 (aromatic CH str.), 1691.6 (C=O),692.23 (C-Cl), 600 (Br); **^{1}H NMR (DMSO, δ (ppm)):** 6.73-8.13 (6H, aromatic ring), 3.40 (3H, CH_3); **R_f value:** 0.28; **Boiling point:** 195^{o}C; **Percentage yield:** 82%.

2.5 Synthesis of KGa

IR (KBr, cm^{-1}): 3058.3 (aromatic CH str.), 1685.5 (C=O),743.7 (C-Cl); **^{1}H NMR (DMSO, δ (ppm)):** 6.85-8.84 (6H, aromatic ring); **R_f value:** 0.28; **Boiling point:** 195^{o}C; **Percentage yield:** 82%.

2.6 Synthesis of KGb

IR (KBr, cm^{-1}): 3058.3 (aromatic CH str.), 1687 (C=O),696.85 (C-Cl); **^{1}H NMR (DMSO, δ (ppm)):** 6.76-8.88 (6H, aromatic ring), 3.41 (3H,CH_3); **R_f value:** 0.28; **Boiling point:** 195^{o}C; **Percentage yield:** 82%.

2.7 Synthesis of KHa

IR (KBr, cm^{-1}): 3060.3 (aromatic CH str.), 1697.8 (C=O),1152.7 (C-F), 720.48 (C-Cl); **^{1}H NMR (DMSO, δ (ppm)):** 6.74-7.84 (6H, aromatic ring); **R_f value:** 0.28; **Boiling point:** 195^{o}C; **Percentage yield:** 82%.

2.8 Synthesis of KHb

IR (KBr, cm^{-1}): 3058.3 (aromatic CH str.), 1696.4 (C=O),1300 (C-F); **^{1}H NMR (DMSO, δ (ppm)):** 6.81-8.68 (6H, aromatic ring), 3.77 (3H, CH_3); **R_f value:** 0.28; **Boiling point:** 195^{o}C; **Percentage yield:** 82%.

2.9 Synthesis of Kia

IR (KBr, cm^{-1}): 3061.6 (aromatic CH str.), 1626 (C=O),1505.6 (NO_2), 692.23 (C-Cl); **^{1}H NMR (DMSO, δ (ppm)):** 6.76-8.89 (6H, aromatic ring); **R_f value:** 0.28; **Boiling point:** 195^{o}C; **Percentage yield:** 82%.

2.10 Synthesis of KIb

IR (KBr, cm^{-1}): 3058.3 (aromatic CH str.), 1737 (C=O),1507.4 (NO_2); **^{1}H NMR (DMSO, δ (ppm)):** 6.94-8.27 (6H, aromatic ring), 3.36 (3H,CH_3); **R_f value:** 0.28; **Boiling point:** 195^{o}C; **Percentage yield:** 82%.

2.11 Synthesis of KJa

IR (KBr, cm^{-1}): 3063 (aromatic CH str.), 1687 (C=O),692.17 (C-Cl); **^{1}H NMR (DMSO, δ (ppm)):** 6.80-8.72 (6H, aromatic ring); **R_f value:** 0.28; **Boiling point:** 195^{o}C; **Percentage yield:** 82%.

2.12 Synthesis of KJb

IR (KBr, cm^{-1}): 3063 (aromatic CH str.), 1668.4 (C=O),692.17 (C-Cl); **^{1}H NMR (DMSO, δ (ppm)):** 6.77-8.73 (6H, aromatic ring), 3.72 (3H,CH_3); **R_f value:** 0.28; **Boiling point:** 195^{o}C; **Percentage yield:** 82%.

2.13 Antibacterial Activity

The synthesized compounds were tested *staphylococcus aureus* (S.A), *E. coli* (E.C) and *pseudomonas aeruginosa* (P.A) bacteria.

The stock solutions of compounds were prepared at a concentration of 5mg/ml & from stock solution the disc were prepared at a concentration of 100µg/ml. The testing was done on muller hinton agar plates by swabbing the agar plates with respective cultures, and placing the disc on it and incubating at 37°C for 24 hrs. the above results were obtained.

2.14 Procedure

1. Label each sterile Petri plate with the name of different bacterium to included (E.coli, P. aeruginosa, S. aureus).
2. Pour the nutrient agar media in the Petri plate when temperatures of media reach about 50^{0}C.
3. Allow the poured Petri plates until it solidify.
4. Spread the 100µl of test micro-organism was inoculated by the spread technique by the spreader.
5. NO: 1 Whattmann filter paper was placed in the pre-labeled agar Petri plate.
6. Each disc was pressed down to insure complete contact the agar surface.
7. Add the 10µl of test sample and 10µl standard sample solvent against the different micro-organism by micro-pipette.

Table 2.1: Antimicrobial Activity of Newly Synthesised Compounds, Zone of Inhibition (Mm), Minimum inhibitory concentration (MIC)

Sample compound	Sovlent	*E.coli* (E.C) Mm µg/ml	*Staphylococcus aureus* (S.A) Mm µg/ml	*Pseudomonas aerug*inosa (P.A) mm µg/ml	MIC Mm µg/ml
LAa	Chloroform	28	27	20	12
LAb	Chloroform	30	30	25	10
LBa	Chloroform	27	31	30	13
LBb	Chloroform	25	20	27	12
LCa	Chloroform	29	25	25	11
LCb	Chloroform	31	28	23	12
LDa	Chloroform	25	24	25	13
LDb	Chloroform	20	31	23	11
LEa	Chloroform	25	24	21	10
LEb	Chloroform	30	26	20	9

3. RESULTS AND DISCUSSION

The Zone of inhibition & Minimum Inhibitory Concentration was determined by the disk plate method. Ceftriaxone was employed during the procedures as reference. The Minimum Inhibitory Concentration the synthesized compounds range between 50-100µg/ml. LAa. LAb, LBa, LBb, LCa, LCb, LDa, LDb, LEa, and LEb were found moderately active, while LAb, LBa, LBb, LCa, LCb, LDa, LDb, , and LEb were found to have more avtivity compared with ceftriaxone. Test compound were found to be more sensitive towords *Staphylococcus aureus, Escherichia coli* and *Pseudomonas aeruginosa*.

4. CONCLUSION

From the date of the Table number 2.1 of anti-microbial activity, it is clearly concluded that the synthesized compounds are promisingly significant, good anti-microbial agents. As per the results of screening it is clearly indicated that the compounds of the scheme have shown good anti-microbial activity equipotent with the standard drugs. This is because of the presence of groups like $–CH_3$, $-NH_2$, -F, -S-, C_6H_5, at the different positions of phenyl nucleus and hetrocyclic system attached to quinazolinone nucleus which is attached to molecule.

From the above results one can establish that the systhesized substituted quinazolinone can be rich source for the exploitation. Therefore in search of new generation of the active compounds, it may be worthwhile to explore the possibility in this area or by making or introducing different functional groups or 2nd amines or by cyclization as substitution. Which may results into better pharmacological agents?

5. ACKNOWLEDGEMENT

This work completed under the guidance of a great researcher in the field of pharmaceuticals. I gratitude to my supervisor Dr. Milind pande, Department of Pharmacy, Institute of Bio-Medical Education and Research, Mangalayatan University for his invaluable guidance and constant encouragement throughout the work. I take this opportunity to express my profound indebtedness to his able guidance.

I take this opportunity to thanks **Mr.Gaurav Garg**, **Lal Ratnakar Singh**, Department of Pharmacy, Institute of Bio-Medical Education and Research, Mangalayatan University for his valuable and moralistic support during this research work.

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